Early acquisition of neural crest competence during hESCs neuralization.

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Authors: Carol Lynn Curchoe, Jochen Maurer, Sonja J McKeown, Giulio Cattarossi, Flavio Cimadamore, Mats Nilbratt, Evan Y Snyder, Marianne Bronner-Fraser, Alexey V Terskikh

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Public Summary:
BACKGROUND: Neural crest stem cells (NCSCs) are a transient multipotent embryonic cell population that represents a defining characteristic of vertebrates. The neural crest (NC) gives rise to many derivatives including the neurons and glia of the sensory and autonomic ganglia of the peripheral nervous system, enteric neurons and glia, melanocytes, and the cartilaginous, bony and connective tissue of the craniofacial skeleton, cephalic neuroendocrine organs, and some heart vessels. METHODOLOGY/PRINCIPAL FINDINGS: We present evidence that neural crest (NC) competence can be acquired very early when human embryonic stem cells (hESCs) are selectively neuralized towards dorsal neuroepithelium in the absence of feeder cells in fully defined conditions. When hESC-derived neurospheres are plated on fibronectin, some cells emigrate onto the substrate. These early migratory Neural Crest Stem Cells (emNCSCs) uniformly upregulate Sox10 and vimentin, downregulate N-cadherin, and remodel F-actin, consistent with a transition from neuroepithelium to a mesenchymal NC cell. Over 13% of emNCSCs upregulate CD73, a marker of mesenchymal lineage characteristic of cephalic NC and connexin 43, found on early migratory NC cells. We demonstrated that emNCSCs give rise in vitro to all NC lineages, are multipotent on clonal level, and appropriately respond to developmental factors. We suggest that human emNCSC resemble cephalic NC described in model organisms. Ex vivo emNCSCs can differentiate into neurons in Ret.k(-) mouse embryonic gut tissue cultures and transplanted emNCSCs incorporate into NC-derived structures but not CNS tissues in chick embryos. CONCLUSIONS/SIGNIFICANCE: These findings will provide a framework for further studying early human NC development including the epithelial to mesenchymal transition during NC delamination.

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